HHS Public Access

Author manuscript

Obstet Gynecol. Author manuscript; available in PMC 2018 February 19.

Published in final edited form as:

Obstet Gynecol. 2016 March ; 127(3): 468–473. doi:10.1097/AOG.0000000000001242.

Risk of Occult Uterine Sarcoma in Women Undergoing Hysterectomy for Benign Indications

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Abstract

OBJECTIVE—To estimate the frequency of unsuspected sarcoma identified postoperatively in women undergoing surgery for benign gynecologic indications at our institution.

METHODS—Patients undergoing hysterectomy for benign gynecologic indications from 2000 to 2014 at our institution were identified. Patients who did not have a preoperative suspicion for malignancy and were found to have uterine sarcoma on pathology postoperatively were considered to have an occult uterine sarcoma. Relevant clinical and pathologic data were collected for this retrospective cohort study.

RESULTS—Ten thousand one hundred nineteen hysterectomies for benign gynecologic indications were performed between 2000 and 2014. Among these, nine patients were found to have uterine sarcoma, with an overall rate 1: 1,124, (95% CI, 1:592, 1:2,457). These malignancies included five leiomyosarcomas, two endometrial stromal sarcomas, and two uterine adenosarcomas. Median age was 39 years (range 25–53). Among women found to have occult sarcoma, hysterectomy was performed as a primary indication for abnormal bleeding (77.8%) and leiomyomas (22.2%). Cases included six total abdominal hysterectomies, two total vaginal hysterectomies, and one supracervical hysterectomy. One case required manual morcellation during abdominal hysterectomy. Power morcellation was not used in any of the cases.

CONCLUSIONS—In summary, occult uterine sarcoma occurs in 0.089% or 1:1,124 hysterectomies for benign indications in our population. The frequency is lower than the rate derived in earlier reports and by the Food and Drug Administration in their pooled analysis.

INTRODUCTION

Hysterectomy is the most common major surgery with almost 400,000 cases for benign indications performed in the United States annually(1). Compared to abdominal hysterectomies, minimally invasive approaches confer a lower risk of perioperative

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Financial Disclosure

The other authors did not report any potential conflicts of interest.

Presented at the American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting on May 3, 2015, San Francisco, California.

complications and quicker recovery (2). However, smaller incisions present the challenge of removing large specimens. The practice of morcellation, has been used for decades, but the introduction of electromechanical morcellators facilitated the removal of tissue during endoscopic procedures (3). The practice has come under scrutiny due to concerns over the inadvertent dissemination of occult malignancies of presumed benign tissue (4, 5). Doing so may worsen the prognosis of uterine sarcoma and confer the need for additional treatment (6, 7). This has led the U.S. Food and Drug Administration (FDA) to issue a safety communication “discouraging the use of power morcellation” and has resulted in changes in surgical practice (8, 9).

The incidence of occult sarcoma in women undergoing hysterectomy is unclear with rates ranging from 1 in 204 to 1 in 667 in women with presumed myomas (10, 11). Risk estimates from the FDA and American College of Obstetricians and Gynecologists range from 1 in 352 to 1 in 500, respectively, for women undergoing surgery for presumed myomas (12, 13). A recent study examining 6360 women undergoing hysterectomy for benign indications found a 1 in 500 risk of sarcoma in this broader group of women(14). To guide patient counseling and clinical practice, we sought to estimate the frequency of unsuspected sarcoma identified in women undergoing hysterectomy for presumed benign conditions at our institution.

MATERIALS AND METHODS

After approval from the University of Texas Southwestern (UTSW) Medical Center Institutional Review Board, all cases of hysterectomy performed for benign gynecologic indications from September 2000 to December 2014 at UTSW Medical Center and Parkland Memorial Hospital were identified from a prospectively maintained departmental billing database which includes all surgeries performed on our campus by UTSW faculty. The database is maintained with quality assurance by a database specialist and searchable through International Classification of Disease codes, Current Procedural Terminology, and faculty names. The database was queried for all hysterectomies performed during this time period. Cases performed for obstetric purposes and for malignancy or suspected malignancies were excluded.

As a designated Academic Comprehensive Cancer Program by the American College of Surgeons’ Commission on Cancer, we utilized the tumor registry of each hospital at UTSW to identify all cases of uterine sarcoma. The tumor registry, which maintains records of all cancer patients diagnosed and treated at the hospital, were queried using the search terms “leiomyosarcoma,” “endometrial stromal sarcoma,” “adenosarcoma,” “undifferentiated sarcoma” and “uterine sarcoma, not otherwise specified.” Carcinosarcoma (previously known as malignant mixed Muellerian tumor) was excluded from this analysis since they are no longer considered pure sarcoma and are considered poorly differentiated carcinoma.

For all uterine sarcoma cases, data regarding clinical presentation, preoperative evaluation, intraoperative findings and pathology were systematically reviewed from the medical record. Unexpected sarcomas were defined as cases where uterine sarcoma were confirmed on surgical pathology, but did not have clinical preoperative suspicion or indication of

malignancy. Because the staging system for uterine sarcoma changed during our study period, we assigned FIGO 2009 sarcoma and adenosarcoma staging systems to all identified occult sarcomas. Relevant clinical and pathologic data were collected from the medical record including symptoms, family history of cancer, preoperative diagnosis, uterine size, imaging studies, surgeon subspecialty, surgical procedure, pathologic findings, further treatment and/interventions, and survival status. Demographics and patient characteristics were summarized using descriptive statistics and Wilcoxan rank sum test was used to compare uterine weights by sarcoma type. Exact Clopper-Pearson (closed form) was used to calculate confidence limits(15). Data analyses were performed using SAS 9.3 (Cary, NC). A p-value <0.05 was considered statistically significant.

RESULTS

Ten thousand one hundred nineteen hysterectomies for benign gynecologic indications were performed during this time period, including abdominal (59.4%), laparoscopic or robotic-assisted (21.6%) and vaginal approaches (18.9%). Among these, nine patients were found to have an unexpected uterine sarcoma, with an overall rate of 1: 1,124 (95% CI, 1:592, 1:2,457). These malignancies included five leiomyosarcomas (LMS), two endometrial stromal sarcomas (ESS), and two uterine adenosarcomas. Thus, in our population, the rate of unexpected LMS is 1:2,024 (95% CI, 1:909, 1:6,250), and 1:5,060 (95% CI 1,401, 1: 41,841) for ESS and adenosarcomas.

The most common primary indications for hysterectomy were leiomyomata (37%), abnormal uterine bleeding (28%), and pelvic organ prolapse (11%). In the cohort of women with occult sarcoma, hysterectomy was performed as a primary indication for abnormal bleeding (77.8%) and leiomyomas (22.2%). 7/9 (77.8%) cases did report either a pelvic mass or uterine myomas as a first or secondary indication.

The average age of women undergoing hysterectomy for benign indications was 45.3 years In the cohort of women found to have an unanticipated sarcoma at the time of hysterectomy, the median age at diagnosis was 39 years (range 25–53); none were post-menopausal. The ethnic make-up was mixed: 4 were Hispanic, 3 were Non-Hispanic White, and 2 were African-American. Median BMI was 27 (range 20–46).

Regarding known or proposed risk factors which may be associated with sarcomas, 2 women were known to have taken combined oral contraceptives, one had been on progesterone-only pills, 4 were not on hormones, and the status of 2 women was unobtainable from chart review. 3 women had been given leuprolide acetate preoperatively; 2 women (1 with LMS, 1 with ESS) experienced improved bleeding and only 1 woman (found to have a LMS) experienced a size reduction in her uterus. None of the women had a history of tamoxifen use or pelvic irradiation, and all denied a family history of cancer. Only 1 patient gave a history of rapid uterine growth; she was a 25 year old woman with increasing abdominal girth over 6 months who was found to have a 52 cm uterus on imaging, ultimately diagnosed with LMS postoperatively.

Preoperative evaluation of the cases included up to date cervical cancer screening in all cases. 2 patients had an ASCUS pap smear with negative high risk HPV testing. Preoperative imaging was obtained in 8/9 cases; 6 had pelvic ultrasound, 1 sonohysterogram and 1 computerized tomography (CT) scan. None of these imaging studies were suspicious for malignancy. 5 women had preoperative endometrial sampling, 4 with normal findings, 1 with insufficient tissue.

All women with occult sarcoma were operated on by obstetrician gynecologist specialists. No cases in which an occult sarcoma was identified was performed by a subspecialist such as female pelvic reconstruction, reproductive endocrinology, or gynecologic oncology subspecialists. The cases included six total abdominal hysterectomies (TAH), two total vaginal hysterectomies (TVH), and one abdominal supracervical hysterectomy (SCH). One patient undergoing TAH required manual morcellation of a large bulky uterus. Electromechanical morcellation was not used in any of the cases. (Table 1).

The one patient who underwent morcellation of an occult sarcoma was a 53-year old found to have a stage IB LMS who underwent TAH, bilateral salpingooophorectomy (BSO), with uncontained manual morcellation of a bulky 1692 g uterus. During the procedure, a suspicious appearing uterine mass was noted and sent for frozen section, which suggested leiomyosarcoma. Intraoperative gynecologic oncology was requested and the abdominal cavity was thoroughly explored with no findings of suspicious disease. She was not upstaged as result of the morcellation. The patient was subsequently treated with 6 cycles of gemcitabine and docetaxel. As of January 2015, she is alive, well, and has had no evidence of disease for 3 years since her surgery.

The 2 uteri found to have ESS weighed 90 and 93 g. The 2 uteri with adenosarcoma uteri weighed 116 g and 225 g. The 5 uteri found to have LMS were significantly larger, with a median weight of 1,692 g (range 144–13,062), p=0.03. The 5 LMS cases were stage IA (1), IB (4); the 2 adenosarcomas were stage IB (1) and II (1); the 2 endometrial stromal sarcomas were stage IA.

Three patients did not receive any additional surgery or treatments outside of observation. 3 patients underwent subsequent BSO, 1 with additional pelvic and para-aortic lymphadenectomy for IB adenosarcoma identified after TVH. 3 patients with Stage IB LMS underwent chemotherapy with gemcitabine and docetaxel.

Two patients had recurrent disease. One patient with Stage IA ESS found after TVH had a subsequent BSO and received postoperative megestrol acetate but was found to have a distant recurrence with pulmonary metastases 7 months after her index hysterectomy, and was treated with letrazole. She was alive with disease 23 months after her index surgery. One additional patient who underwent TAH/BSO found to have stage IB LMS also had a recurrence. She underwent posterior exenteration, chemotherapy with gemcitabine and docetaxel, radiation treatment, and died within 23 months after her index hysterectomy. The remaining 7 patients with occult sarcomas, including the patient who underwent manual morcellation during TAH, were known to be alive with no evidence of disease over a median follow up of 48 months (range 12–135 months).

DISCUSSION

Uterine sarcomas are a relatively rare, potentially aggressive, heterogeneous group of gynecologic malignancies. Sarcomas have been challenging to diagnose prior to surgery due to limitations in clinical and radiographic predictors. Because of the frequency with which hysterectomies are performed, accurate assessment of the incidence of occult malignancies encountered during surgery for suspected benign gynecologic conditions is important for various reasons, including counseling regarding the risks and benefits of surgical approach, appropriate surgical planning, and avoidance of iatrogenic complications.

Our finding of the incidence of unexpected sarcoma at the time of hysterectomy is on the lower end of estimates previously reported. This rate is lower than a recent report using a statewide database examining the occult malignancy rate in women undergoing hysterectomy in Michigan(14). The different findings likely reflect differences in the study populations. In both instances, the overall low rates of occult sarcoma may also be due to inclusion of a broader group of patients undergoing hysterectomy, not limited to those only with presumed myomas.

Previously reported rates of occult sarcoma have ranged from 0 to 1:204 (11, 16) in analyses limited to women with presumed myomas, which may confer a higher likelihood of sarcoma. When developing their recommendations, the FDA used available reports of occult sarcoma in a pooled analysis to derive an estimate of 1:352 risk of occult sarcoma in women undergoing hysterectomy or myomectomy for presumed myomas. Their estimate has been criticized based on concerns about the quality of the data of the 9 studies included, as well as the potential for publication bias and inclusion of only retrospectives studies (17–19). The largest study in the pooled analysis included only 1429 patients. Furthermore, mixed populations including women undergoing hysterectomy and myomectomy were used to derive the risk estimate, and some studies also included referral patients which may have elevated the risk. This methodology may have additional flaws since the indications for myomectomy are different from those for hysterectomy, and thus the populations, age distribution, and incidence of occult malignancy in the two groups vary (20, 21). Though many of the studies used by the FDA in their pooled analysis were from university hospitals and referral centers much like ours, they were not able to describe clinically relevant factors such as preoperative evaluation and postoperative care and outcomes(18).

During the study period, there were 64 cases of preoperatively clinically suspected uterine sarcoma in which the primary surgery was performed at our institution. Of the 64 uterine sarcomas, there were 28 LMS, 14, ESS, 13 high grade uterine sarcomas, and 9 adenosarcomas. Sarcoma cases that were referred only for postoperative management were excluded from this analysis.

Of note, all occult sarcoma cases in our study were found in patients who were receiving their primary gynecologic care at our institution, not amongst women referred for subspecialty care. All patients had received up to date cervical cancer screening and in the majority of cases, women had received preoperative evaluation with either endometrial sampling or imaging which did not suggest malignancy. Of the suggested risk factors for

sarcoma, it is notable that none of the women we identified were post-menopausal, exposed to pelvic radiation or tamoxifen, nor had a family history of cancer. The average age of women undergoing hysterectomy at our institution was younger than that in the Michigan study, and our finding of a relatively young cohort of women with sarcoma is unexpected and contrary to expectations of age-related risks (13, 21). The absence of these risk factors may be related to why these patients were not referred to gynecologic oncologists and were not suspected to have sarcomas preoperatively.

A strength of our study is that we were able to determine the postoperative outcomes of these patients to a median of 48 months after hysterectomy. 6 of the 9 patients underwent additional interventions with either additional surgery, chemotherapy, radiation therapy or a combination of these. Data are limited to guide the postoperative management of such occult cases, thus management should be individualized to each case. Notably, the patient who did experience manual morcellation of an LMS completed 6 cycles of chemotherapy and has been followed to 49 months since her hysterectomy with no further evidence of disease. The major disadvantage of our study is it is retrospective, with the inherent biases, including misclassification and missing data, which may limit the findings. Given the rarity of uterine sarcomas, prospective studies may be challenging to perform at a single institution.

The relatively low rates of occult uterine sarcoma derived from ours and other recent studies may be useful for counseling patients about management options and surgical planning during hysterectomy(14). Yet it is important to stress that although low, the risk of encountering an occult sarcoma exists. Hence ongoing efforts to identify potentially safer methods for tissue extraction are essential, as are efforts to improve preoperative identification of malignancies.

In summary, occult uterine sarcoma was identified in 1:1,124 hysterectomies for benign indications in our population. The frequency is lower than the rate derived in earlier reports and by the FDA in their pooled analysis.

Acknowledgments

The authors thank Rebecca Pederson for her assistance with data collection.

Supported by the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center.

Kimberly Kho has served on the study protocol advisory panel for Acatmax Surgical Materials, LLC, and has served as primary investigator on a research grant involving educational simulation materials for Applied Medical. Debra Richardson has served on the advisory boards of Astra Zeneca and Genentech.

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Table 1

Cases of occult sarcoma identified during hysterectomy for benign gynecologic conditions.

Patient	Age (years)	Race	BMI	1′ Dx	Surgery	Uterine weight (g)	Sarcoma type	Stage	Treatment	Status	Follow up (mo)
1	25	White	46	Pelvic mass, leiomyomas	TAH/USO	13,062	LMS	IB	Chemo	NED, alive	12
2	50	Black	42	AUB	SCH	590	LMS	IB	Observation	NED, alive	135
3	47	White	25	AUB, leiomyomas	TAH/BSO	2395	LMS	IB	-Posterior exenteration -Chemo -RT	Recurred, dead	23
4	39	Hispanic	27	AUB, leiomyomas	TAH/BS	144	LMS	IA	Observation	NED, alive	53
5	53	Black	30	AUB, leiomyomas	TAH/BSO with manual morcellation	1692	LMS	IB	Chemo	NED, alive	49
6	39	Hispanic	27	AUB, leiomyomas	TAH	91	ESS	IA	-BSO -hormonal therapy	Recurred, alive	23
7	39	Hispanic	20	AUB, leiomyomas	TVH	93	ESS	IA	BSO	NED, alive	36
8	37	Hispanic	26	AUB, leiomyomas	TVH	116	Adenosarcoma	IB	BSO, PPALND	NED, alive	48
9	44	White	33	AUB	TAH/BSO	225	Adenosarcoma	IA	Observation	NED, alive	103

BMI=body mass index; 1′ Dx = primary diagnosis; TAH= total abdominal hysterectomy; USO−= unilateral salpingo-oophorectomy; LMS = leiomyosarcoma; Chemo=chemotherapy; NED = no evidence of disease; AUB=abnormal uterine bleeding; SCH= supracervical hysterectomy; BSO= bilateral salpingo-oophorectomy; RT=pelvic irradiation; BS= bilateral salpingectomy; ESS = endometrial stromal sarcoma; PPALND=pelvic and paraaortic lymphadenectomy